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Asymmetric Reduction of α -Keto-esters and Trifluoroacetophenone with *N*-anionized Hantzsch ester

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In the Grignard reagent-catalyzed reduction of carbonyl substrates with the Hantzsch ester, the *N*-anionization of the reductant prior to the hydrogen transfer to the substrate was unequivocally established by the deuterium-labelling experiments. By virtue of this system, asymmetric reductions of carbonyl compounds was effected with the enantiomeric excess ranging over 23–67 %.

KEY WORDS: Asymmetric reduction / *N*-Anionized Hantzsch ester / Trifluoroacetophenone / α -Keto-ester / NADH model reaction /

In a previous communication,¹⁾ we reported that the direct transfer of hydrogen from the Hantzsch ester to carbonyl substrates was accelerated by the mono-ionized zinc species in the Reformatsky mixture and a high asymmetric yield was obtained in an asymmetric double induction.

We describe here the analogous reductions of carbonyls with the Hantzsch ester, which were effected by the Grignard reagent catalysis instead of the Reformatsky mixture, and discuss the mechanistic role the metal plays in the present NADH model reaction system.

It was in 1967 that the Russian workers²⁾ for the first time found the effective catalysis of metal species such as metal alcoholate and the Grignard reagent in the reduction of fluorenone and benzophenone by the Hantzsch ester. The maximum yield recorded was 70 % in the system involving the Hantzsch ester, fluorenone, sodium ethoxide and glucose but the yield with the use of the Grignard reagent declined to 5–7 %.

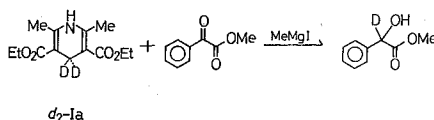
However, this study has since been ignored and neither reinvestigation nor development has been made to date. Nonetheless, in view of the fact that the Hantzsch ester has been as widely used as the dihydronicotinamide derivatives in the NADH model reactions, it seemed of significance to improve the reactivity of the Hantzsch ester by the optimization of reaction parameters.

To this end, we investigated the reduction of α -keto-esters and trifluoroacetophenone with the Hantzsch ester in the presence of the Grignard reagent.

First, the direct transfer of hydrogen from the C-4 position of dihydropyridine ring to substrate carbonyl was confirmed by the reduction of benzoylformate with 4,4-dideuteriated Hantzsch ester (*d*₂-Ia) in the Grignard solution to give deuterio-mandelate. The reduction product mandelate- α -*d* thus obtained in 23 % chemical

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Scheme 1

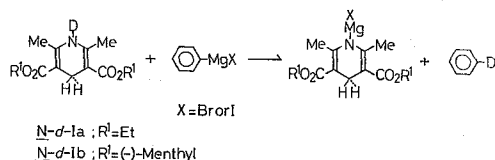


yield was of 83 % isotopic purity. (scheme 1)

Then, in order to establish the intermediate formation of a dihydropyridine-N-MgX species, we designed and carried out the following experiment (scheme 2). The *N*-deuterated Hantzsch ester (*N-d-1a* or *N-d-1b*) was added to phenylmagnesium bromide or iodide. After 5 min's stirring, the reaction was quenched by the addition of water (run 1, 2 and 3 in Table I). The vpc and gc-mass analyses showed that benzene was recovered in 71–80 % yield based on phenyl halide used. Biphenyl was also isolated from the reaction mixture in 12 % (run 2) and 22 % (run 3) respectively in terms of benzene. No traces of unreacted phenyl bromide was detected at all in run 3. Consequently the recovery of products in terms of benzene amounted to 92 % and 93 % in runs 2 and 3 respectively and may well be regarded as nearly quantitative in all three runs.

Furthermore, gc-mass analysis showed the isotopic purity of the recovered deuteriobenzene to be 73,69 and 71 %, so that the net recovery of isotopically pure deuteriobenzene was 58,55 and 50 % in runs 1,2 and 3 respectively. These data are apparently not convincing enough for the establishment of the proposed Grignard exchange reaction (scheme 3) on the basis of monodeuterated benzene formed, so that designed was an alternative experiment; the quenching reaction by deuterium oxide at the stage of the Grignard reagent. Thus, as can be seen from the data in run 4 (Table I), biphenyl and non-deuterated benzene were formed in 9 and 7 %

Scheme 2

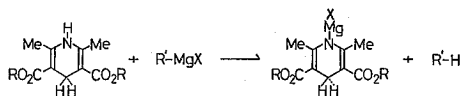
Table I. Quenching of *N*-anionized Hantzsch ester and the Grignard reagent.

run	Hantzsch ester	Grignard reagent	% Yield				recovery
			$\text{C}_6\text{H}_5\text{-D(I)}$	$\text{C}_6\text{H}_5\text{-H(II)}$	(I)+(II)	biphenyl ^{a)}	
1	<i>N-d-1a</i>	PhMgBr	58	22	80	—	—
2	<i>N-d-1a</i>	PhMgI	55	25	80	12	92
3	<i>N-d-1b</i>	PhMgBr	50	21	71	22	93
4	—	PhMgBr	64	7	71	9	80

a) Calculated in terms of benzene.

Asymmetric Reduction with *N*-anionized Hantzsch Ester

Scheme 3



yields respectively already at the stage of the Grignard formation and the yield of deuteriobenzene was 64 %.

The difference in recovery of deuteriobenzene, non-deuterated benzene and biphenyl between the former three runs and run 4 seemed to be slightly beyond experimental errors.

However, this apparent difference, not to be neglected, is cogently rationalized by invoking the possible occurrence of hydrogen abstraction from the solvent medium and the Grignard coupling of phenyl radical which resulted in the formation of non-deuterated benzene and biphenyl respectively at the stage of the Grignard exchange reaction with Hantzsch ester. Another factor to be taken into account for the balance sheet of products is the accuracy of pmr-analysis, with which the isotopic purity of *N*-deuterated Hantzsch ester was assessed to be 100 %. The peak of the *N*-proton signal in pmr spectrum was actually too feeble to permit enough reliable integration by all means.

It may well be deduced, therefore, that the *N*-anionized Hantzsch ester was formed by the Grignard exchange reaction really in no less than 70 % yield, which surpassed by far the values based on isolated deuteriobenzene. So that the Hantzsch ester was nearly completely anionized in the Grignard solution.

Despite the fact that the metal species is indispensable for the NADH model systems in general and also profoundly affects the asymmetric synthesis,³⁾ its function has been obscure as yet. The Lewis acid catalysis to activate the carbonyl group has been the sole claim so far. Ohno *et al.* argued against this view and suggested the possibility of the activation of hydrogen donor by metals,⁴⁾ although convincing experimental evidence has not been presented.

Now, we may conclude that so far as the present system is concerned, the metal activates the hydrogen donor through *N*-anionization, though the possibility of the concurrent activation of substrate carbonyl cannot necessarily be excluded at all. The metal is capable of donating electron to the dihydropyridine ring through the polarized N-Mg bond and the dihydropyridine thus enriched in electron is prone to promote the C-H bond fission or charge transfer complex formation.⁵⁾

Scheme 4

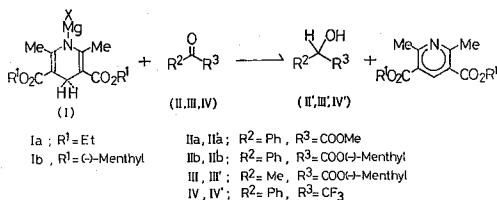


Table II. Asymmetric reduction of α -keto-esters and trifluoroacetophenone with the Hantzsch esters.

run	Hantzsch ester	Substrate	Grignard reagent	Solvent	Period (hr)	Temp.	Product carbinol			
							% Yield	$[\alpha]_D^{20}$	Config.	% Asymmetric Yield
1	Ib	IIa	MeMgI	Et ₂ O	20	reflux	quant.	-39.8	R	23 ^{a)}
2	Ia	IIa	MeMgI	Et ₂ O	20	reflux	40	—	R	28 ^{b)}
3	Ia	IIa	PhMgBr	Et ₂ O	3	reflux	50	—	R	33 ^{b)}
4	Ib	IIb	MeMgI	Et ₂ O	20	reflux	quant.	—	R	48 ^{b)}
5	Ib	IIb	PhMgBr	Et ₂ O	3	R.T.	42	—	R	55 ^{b)}
6	Ib	IIIb	PhMgBr	Et ₂ O	20	R.T.	15	—	R	65 ^{b)}
7	Ib	IV	PhMgBr	THF	1	-2°C	90	-8.73	R	67 ^{c)}
8	Ib	IV	BzMgCl	THF	1	-2°C	75	-5.31	R	40 ^{c)}
9	Ib	IV	PhMgBr	Et ₂ O	1	-2°C	80	-7.27	R	54 ^{c)}
10	Ib	IV	BzMgCl	Et ₂ O	1	-2°C	38	-7.15	R	55 ^{c)}

a) Based on the reported maximum rotation¹¹⁾ of methyl mandelate; $[\alpha]_D^{18} \pm 173^\circ$ (benzene).

b) By the direct vpc-determination of the diastereomer formed^{13), 14)}.

c) Based on the reported maximum rotation¹²⁾ of (*R*)-trifluoromethylphenylcarbinol; $[\alpha]_D^{10} - 13.1^\circ$ (benzene).

Subsequently we undertook the asymmetric synthesis in the present system by virtue of the Grignard reagent catalysis, to know whether or not the asymmetric bias be affected by the kind of halogen in the Grignard reagent used. (scheme 4)

As can be seen from the data collected in Table II, both the enantioselective and diastereoselective reductions of benzoylformates with chiral and achiral Hantzsch esters gave (*R*)-mandelates in 23–33 % e.e. when (–)-(3*R*)-menthol was used as chirality inducer. (runs 1,2 and 3)

Remarkable increments in e.e. were observed in asymmetric double induction; *i.e.* from 23 % (run 1) and 28 % (run 2) to 48 % (run 4) and from 33 % (run 3) up to 55 % e.e. (run 5). This was also the case with pyruvate (run 6), in which a satisfactory e.e. (65 %) was attained. Trifluoroacetophenone was proved to be a good substrate in the present asymmetric system as well and the product carbinol was obtained in as high an yield as 90 % and 40–67 % e.e., which are well comparable with those reported so far in literatures.⁶⁾

It is to be noted that the enantioselectivity of the chiral Hantzsch ester was manifested unexceptionally at the *si*-face of the substrate carbonyl irrespective of the kind of substrate (IIa and IV) and the Grignard reagent. (runs 1 and 7–10) The same trend was observed also in the diastereoselective reactions (runs 2 and 3) which afforded the *R*-mandelate ester in preponderance. In addition, (–)-(3*R*)-menthyl groups, when incorporated as chirality-inducing center in both reactants, cooperated to direct the steric course of the double induction systems (runs 4 and 5) in the same sense, as clearly reflected in the much-improved asymmetric yield of the same *R*-enantiomer as in the individual inductions.

These stereochemical results found for the present asymmetric system were in complete agreement with those obtained in our previous studies of asymmetric reductions of α -keto esters with the Hantzsch esters catalyzed by the Reformatsky mixture.¹⁾

In view of the stereochemical outcome in the present and the previous asymmetric systems that the unexceptionally predominant *si*-face attack of the Hantzsch esters took place with higher stereoselectivity, whose direction and magnitude were not significantly affected by the modifications of the reaction parameters such as solvent medium, metal species, temperature and halide, it seems very likely that the present NADH model reduction with the Hantzsch ester proceeds *via* such a rigid transition state as to meet rigorous stereochemical requirements.

After the stereochemical model proposed by Prelog⁷⁾ for the relative orientation of reductants to substrates in the reduction of NADH-dependent alcohol dehydrogenase, any stereomodel could be arbitrarily devised for accommodating the stereochemical results in the present asymmetric Hantzsch ester reductions as well by taking into account merely the steric factors. But we would rather prefer leaving the transition state topology open to providing an *ex post facto* explanation based on insufficient data available for the present time. More accumulation of knowledge is needed for a better understanding of the steric course of the present asymmetric reduction with the Hantzsch ester.

EXPERIMENTAL

Pmr, uv, ir and gc-mass spectra were recorded on Varian EM-360, Union Giken SM-401, Hitachi 215 and Varian NEVA TE-600 spectrometers, respectively. The optical rotation was measured with Perkin-Elmer 241 polarimeter. Vpc analysis was performed on Shimadzu gas chromatograph GC-4CM and preparative vpc on Varian Aerograph Model 920.

Reductants: 2,6-Dimethyl-3,5-dicarbo-(—)-menthoxy-1,4-dihydropyridine (Ib) was prepared as follows. According to Hantzsch method,⁸⁾ aqueous formaldehyde (37 %, 8.7 g, 107 mmol) and 20 drops of diethylamine were added to menthyl acetoacetate⁹⁾ (49.0 g, 204 mmol) and allowed to stand for 60 hr. After the period, the reaction mixture was extracted with ether and the combined extracts was evaporated. To this residue was added an equal volume of ethanol. Ammonia gas was passed through the chilled solution until saturation. The solution was allowed to stand at room temperature for 60–70 hr and then evaporated to dryness.

The residue was crystallized from ethanol/water. Further two recrystallizations afforded 13 g of pale yellow crystal, mp 159–161°C. $[\alpha]_D^{30.5} = -94.0^\circ (c\ 10.96, CHCl_3)$. Pmr $\delta_{TMS}^{CDCl_3}$: 0.5–2.4 (36H, m, protons in menthyl moiety), 2.3 (6H, s, —CH₃ on pyridine nucleus), 4.6–5.2 (2H, m, hydrogens on carbinol carbons), 5.6 (1H, s, N-H). Ir $\max^{KBr} cm^{-1}$: 760, 1120, 1210, 1300, 1370, 1380, 1500, 1670, 1700, 2870, 2930, 2950, 3350 (N-H). Uv (EtOH) 375 nm (ϵ , 6.8×10^3). Anal. Calcd. for C₂₉H₄₇NO₄: C, 73.53; H, 10.00; N, 2.96. Found: C, 73.34; H, 10.05, N, 3.02 %.

4,4-Dideuterio-2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine (*d*₂-Ia) was prepared in the same manner as described above by the use of *d*₂-deuterioformaldehyde in place of formaldehyde. The isotopic purity of the deuterated dihydropyridine at the C-4 position was determined to be complete by pmr-monitoring of the signal assignable to the protons on C-4 position of the ring.

N-Deuterio-2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine (*N-d*-Ia) and *N*-deuterio-2,6-dimethyl-3,5-dicarbo-(—)-menthoxy-1,4-dihydropyridine (*N-d*-Ib) were prepared by refluxing Ia or Ib in D₂O/THF repeatedly three times according to the literature procedure¹⁰⁾ and the deuteration on the *N*-position was determined to be complete by pmr-monitoring of the signal to be assigned to the proton on *N*-1-position.

Reduction of methyl benzoylformate with 4,4-dideuterated Hantzsch ester: A solution of methylmagnesium iodide was prepared by dropwise addition of methyl iodide (186 mg, 1.3 mmol) to a stirred suspension of magnesium turnings (25 mg, 1.1 mmol) in absolute ether (10 ml) under argon and aged for 30 min. 4,4-Dideuterated Hantzsch ester (270 mg, 1.06 mmol), (*d*₂-Ia) was added to the Grignard solution, upon which the yellow color of *d*₂-Ia instantly turned intense orange and the solution heterogeneous. In instant succession, was added methyl benzoylformate (164 mg, 1.0 mmol) and the solution was refluxed in the dark under argon overnight. After 24 hr, the reaction was quenched with 2N hydrochloric acid. The aqueous layer was extracted three times with ether. The combined extracts

was washed once with 2N sodium bicarbonate solution, three times with water and dried over magnesium sulfate. The solvent was removed and the residue was chromatographed on silica gel with benzene used as eluent. After further purification by preparative vpc (15 % polyethyleneglycol succinate, 6 m, 180°C), pure product was obtained (38 mg, yield 23 %). The isotopic purity of methyl mandelate was assessed to be 83 % by comparison with the integral values of carbinol methine peak in pmr spectrum.

Quenching of the Grignard reagent with *N*-deuterated Hantzsch ester:

General experimental procedure of the quenching reaction of the Grignard reagent with *N*-deuterated Hantzsh ester was exemplified by the typical run 3 in Table I.

Phenylmagnesium bromide was prepared in the usual manner from magnesium powder (120 mg, 5.0 mmol) and bromobenzene (785 mg, 5.0 mmol) in dry ether (50 ml) and aged for 30 min. *N*-Deuterio-2,6-dimethyl-3,5-dicarbo-(—)-menthoxy-1,4-dihydropyridine (2417 mg, 5.1 mmol) was added to the Grignard solution at room temperature, upon which an intense orange precipitate resulted.

After 5 min's stirring, the reaction mixture was quenched with hydrochloric acid (10 ml) and saturated with sodium chloride. The aqueous layer was extracted with three 20 ml-portions of ether. The combined extracts was washed two times with water and made up to 100 ml, which was subsequently analyzed.

The yield of benzene was gas-chromatographically determined to be 71 % in reference to the standard calibration curve (15 % Carbowax 20M, 6 m, 50°C).

Biphenyl, detected by gc-mass (1.5 % OV 101, 2 m, 120°C), was gaschromatographically (15 % polyethyleneglycol succinate, 1 m, 130°C) determined. Yield, 22 % in terms of benzene. Mass spectrum (*m/e*, 156) was identical in every respect with that of the authentic sample.

The isotopic purity was calculated to be 71 % by the comparison of the relative intensity of fragmentation peaks of sample with those of authentic benzene. (run 3 in Table III)

The isotopic purity and relative peak intensity of the benzene in runs 1 and 2 in

Table III. Isotopic purity and relative peak intensity of benzene products.

run ^{a)}	Isotopic ^{b)} purity	Relative peak intensity ^{c)}		
		M^+ (<i>m/e</i> 79) [M^+ (<i>m/e</i> 78)] ^{d)}	$M^+ - 1$ (<i>m/e</i> 78) [$M^+ - 1$ (<i>m/e</i> 77)]	$M^+ - 2$ (<i>m/e</i> 77) [$M^+ - 2$ (<i>m/e</i> 76)]
1	73%	100 [100]	61 [29]	18 [7]
2	69%	100 [100]	73 [29]	18 [7]
3	71%	100 [100]	63 [28]	21 [10]
4	89%	100 [100]	35 [28]	10 [8]

a) Each run corresponds to that in Table I.

d) Corrected for natural isotope abundance according to Biemann.¹⁵⁾

c) Base peaks in all 4 runs were identical with parent peaks.

b) Values in parentheses showed the corresponding relative peak intensity of authentic benzene.

Table 1 were also collected in Table III.

Quenching of the Grignard reagent with deuterium oxide: Phenylmagnesium bromide from magnesium (480 mg, 20 mg-atom) and bromobenzene (3.14 g, 20 mmol) in ether (50 ml) was prepared in the usual fashion under argon.

After 30 min's aging at room temperature under argon, deuterium oxide (5 ml) was added to the Grignard solution and stirred for further 5 min. After the same work-up as for run 3, ethereal solution (100 ml) for estimation was obtained. Subsequent vpc and gc-mass analyses were performed as described in run 3. The yield of benzene was 70 % and only a trace of bromobenzene peak was detected. The isotopic purity of benzene, 89 % and its relative intensity of fragmentation peak were shown in run 4 in Table III.

Biphenyl was also obtained. Yield, 9 %.

General experimental procedure for asymmetric reductions: a) Experimental procedure applied for runs 1 and 7-10 in Table II was exemplified by a typical run 9. A solution of phenylmagnesium bromide was prepared in the usual manner from bromobenzene (785 mg, 5 mmol) and magnesium (120 mg, 5 mg-atom) in dry ether (50 ml).

After 1 hr, the reaction mixture was quenched, extracted and concentrated with strict adhesion to the experimental manner of direct hydrogen transfer with deuterated Hantzsch ester (*vide supra*).

Chemical yield was determined at this stage by the comparison of vpc chromatograms (15 % polyethyleneglycol succinate, 4 m, 150°C) of the products with those of an authentic sample. Yield, 80 %. Purification by column chromatography (silica gel, benzene) and subsequently by preparative vpc (15 % polyethyleneglycol succinate, 6 m, 170°C) afforded the pure product, $[\alpha]_D -7.27^\circ$ (c 4.78, benzene), 54 % e.e..

b) Experimental procedure for runs 2-6 was typically exemplified by run 3. Phenylmagnesium bromide was prepared from magnesium (29 mg, 1.2 mg-atom) and bromobenzene (204 mg, 1.3 mmol) in anhydrous ether (50 ml). To the Grignard solution thus formed, 2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine (370 mg, 1.5 mmol), (Ia) and (–)-menthyl benzoylformate (288 mg, 1.0 mmol), (IIb) were successively added and the solution was refluxed in the dark under argon overnight. After 3 hr, the reaction mixture was quenched, extracted, dried and concentrated to a small volume (10 ml).

At this stage, not only the chemical yield was determined to be 50 % by vpc comparison (5 % Carbowax 20M, 4 m, 160°C) with an authentic sample, but also the absolute configuration and the asymmetric yield were determined by comparison with authentic samples of (–)-menthyl-(*R*)- and (*S*)-mandelates (II'b). By this means, the *R*-configuration was assigned to the predominant diastereomer of product mandelate with an asymmetric yield of 33 %.

Exactly the same vpc determination was applied also for run 6, and the *R*-configuration and the asymmetric yield (65 % e.e.) were obtained.

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